EXHIBIT 8

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90/007,542	05/13/2005	6331415	22338-10230	7585

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Please find below and/or attached an Office communication concerning this application or proceeding.

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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/007,542*.

PATENT NO. *6331415*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/007,542	Patent Under Reexamination 6331415	
	Examiner Bennett Celsa	Art Unit 3991	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

a☒ Responsive to the communication(s) filed on *21 May 2007*. b☒ This action is made FINAL.
c☐ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-36* are subject to reexamination.
1b. ☐ Claims _____ are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☐ Claims _____ are patentable and/or confirmed.
4. ☒ Claims *1-36* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____.
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

Reexamination of US Patent No. 6,331,415 (Cabilly 2 patent).

Status of the Claims

Claims 1-36 are pending and under reexamination. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Procedural Posture:

Merger of 3rd Partly Requests 90/007,542 and 90/007,859

	i. 90/007542 ('7542 Proceeding):	ii. 90/007859 ('7859 Proceeding)
Reexamination request filed:	5/13/05	12/23/05
Reexamination ordered:	7/7/05.	1/23/06
Patent Owner Statement:	none	none
First Office Action mailed:	9/13/05	N/A
Patent Owner Response dated	1/25/05	N/A
'7542 AND '7859 merged:	6/6/06	

Following merger of the 90/007,542 and 90/007,859 proceedings, the First Office Action dated September 13, 2005 in the '7542 proceeding was withdrawn in light of the Non-Final Office Action dated August 16, 2006.

Patent owner's November 25, 2005 response (with Declarations) and October 30, 2006 response (with Declarations) to the September 13, 2005 and subsequent August 16, 2006 office actions, respectively in the 90/007,542 proceeding were filed.

Final rejection of claims 1-36 was mailed February 16, 2007 including raising a new ground of rejection over the Moore 5,840,545 patent included in the IDS submitted December 14, 2006 and January 16, 2007 information disclosure statements.

A Patent Owner Response After-Final rejection (dated 5/21/07) that included:

a. 132 Declarations by Michael Botchan, Steven Lanier McNight, Mathhew P. Scott, and Sidney Altman;
b. An Information Disclosure Statement (IDS);
c. A Confidential Information Disclosure Statement (Artifact Sheet);
d. Exhibit B (54 pages) Moore 06/358,414 application with original claims 1-25; and
e. 181/182 Petition and Renewed Petition to Reopen Prosecution To Withdraw Finality or alternatively for the Filing of a Request for Continued Reexamination (RCR) is acknowledged.

The Petition decision of June 1, 2007 resulted in the granting of this RCR. The finality of the February 16, 2007 Office Action is hereby withdrawn, and the prosecution is reopened for consideration of the patent owner May 21, 2007 response and Declaration submissions.

Information Disclosure Statement (IDS)

The 9/6/07 IDS submitted listing references on a PTO-1449 has been considered as indicated by the enclosed Examiner-initaled copy. It is to be noted, however, that consideration by the examiner of the information submitted in an IDS means nothing more than considering the documents in the same manner as other documents in Office search files are considered by the examiner while conducting a search of the prior art in a proper field of search. See MPEP 609, at page 600-125, Revision 2, May 2004.

Information Submitted Under MPEP § 724.02 in Petition Under 37 CFR 1.59 (b) and 1.182 (expunge) and 1.183 (3rd Party service):

The owner has submitted papers on 5/21/07 and 10/24/07 deemed confidential and/or proprietary along with a petition for expungement of this material and director waiver of the 37 CFR § 1.550(f) 3rd party service requirement.

On October 9, 2007, the petition under 37 CFR 1.183 to waive the 3rd party service requirement was granted and the submitted documents provisionally sealed pending a materiality determination regarding the expungement of these documents.

Pursuant to MPEP § 724.04 the submitted information is found immaterial to the patentability and/or confirmation of the instant reexamination claims.

Priority

The 6,331,425 (Cabilly 2) patent undergoing reexamination issued on December 18, 2001 from application 07/205,419 (filed 6/10/88) which was a continuation of 06/483,457 (filed 4/8/83) now the 4,816,567 (Cabilly 1) patent.

Withdrawn Objection (s) and/or Rejection (s):

The following rejections raised in the February 16, 2007 office action are hereby withdrawn for the following reasons:

1. Claims 1-7, 9-10, 14-18 and 21, 23-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Moore et al. U.S. Pat. No. 5,840,545 (Nov. 24, 1998: effective filing date of March 15, 1982 of date of 06/358,414).

2. Claims 1-7, 9-10, 14-21 and 23-36 rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-10, 14-18, 21 and 23-36 alone, or if necessary further in view of Axel et al. U. S. Pat. No. 4,399,216 (Aug. 1983: filed Feb. 25, 1980) as applied against claims 19-20.

3. Claims 1-7, 9-10, 14-18 and 21-36 rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-10, 14-18 and 21, 23-36 and in view of Accolla et al. PNAS USA 77(1) 563-566 (January 1980) as applied against instant claim 22 (anti-CEA antibody).

4. Claims 1-7, 9-11, 13-18, 21 and 23-36 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) and Moore et al. U.S. Pat. No. 5,840,545 (Nov. 24, 1998: effectively filed March 15, 1982).

5. Claims 1-7, 9-11, 13-21 and 23-36 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) and Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-11, 13-18, 21 and 23-36 and further in view of Axel et al. U. S. Pat. No. 4,399,216 (Aug. 1983: filed Feb. 25, 1980) as applied against instant claims 19-20 (mammalian host cell).

6. Claims 1-7, 9-11, 13-18 and 21-36 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) and Moore et al. U.S. Pat. No. 5,840,545 as applied above against claims 1-7, 9-11, 13-18, 21 and 23-36 and in view of Accolla et al. PNAS USA 77(1) 563-566 (January 1980) applied against instant claim 22.

The above six rejections relying upon the Moore'545 patent claim teaching of single host expression of antibody variable chains is withdrawn for reasons discussed *infra*. Additionally, the vector constructs and corresponding host of instant claims 15-17 that require "different insertion sites" for the variable antibody heavy and light chains are not anticipated by the Moore vector construct that inserts its variable regions at the same pstI restriction site (see Moore col. 23, lines 35-45).

Teachings of the Moore 5,840,545 disclosure and patent claims 1-2 with respect to the 06/358, 414 application (filed March 15, 1982)

Patent Owner Evidence: includes;

a. Arguments in 5/21/07 owner response pages 7-20:

b. Submitted Declarations of: Drs. Altman, Botchan McKnight and Scott:

c. Copy of Dr. Yarranton Declaration submitted as paper no. 27, dated April 3, 1996 from 08/165,530 application (issued as Moore 5,965,405 patent).

Examiner Holding:

Upon review of the 5,840,545 patented claims and file patent history along with the patent owner submitted 132 declarations, the Examiner finds that the '545 patented invention and accompanying disclosure describes and enables expression, using two vectors, of light and heavy antibody chains comprising variable regions in *separate* prokaryotic (E. Coli) or eukaryotic (yeast) host cells for producing an assembled functional single-chain antibody (Fab or Fv) as of March 15, 1982.

However, the Moore '545 patent claims encompassing *single host expression* of variable light and heavy chain for producing single-chain antibody are only entitled to the June 5, 1995 date since the original 06/358,414 specification and claims 1-25 only disclose the separate expression of the heavy and light chain antibody fragment in different host cells as pointed out by the patent owner on pages 13-14 of the 5/21/07 response.

In this regard, the *Moore* '545 patent claims 1-2 were first presented as new claims 32, 34 and 35 in the *June 5, 1995* preliminary amendment (copy enclosed) in the *Moore* 08/461,071 application, which later issued as the Moore '545 patent.

Newly presented *Moore* application claims 32 (A recombinant double-chain antibody fragment) and 34 (host) correspond to Moore issued patent claim 1, whereas claim 35 corresponds to Moore issued claim 2.

Support for the preliminary amendment, and new claims 32, 34 and 35 was asserted by Moore (through his attorney) to be:

a. "generally based on the claim set of ancestor (sic) application, 06/358,414, filed March 15, 1982";
b. "Support for the recital of host cells is provided at, e.g., p. 8, last paragraph of the specification"; and
c. "The process for 'tailoring' a cloned DNA to remove the part encoding the constant region is described at, e.g., pp. 10-15 of the application".

However, no support for single host expression of variable light and heavy chains was found for new claims 32, 34 and 35 in the 06/358,414 application filed March 25, 1982.

Patent Owner Arguments w/r to Moore '545 Patent and Examiner Rebuttal:

1. Patent Owner: *Moore* fails to disclose eukaryotic yeast host cell expression stating:

> Moreover, the Moore '545 patent contains no description of a non-bacterial host cell being used to produce light or heavy chain variable region polypeptides. The passage cited by the Office (i.e., col. 5, lines 47-52 of '545 patent) at best suggests that a yeast cell could be a host cell that could be used to amplify cDNA obtained from a cDNA library. There is no discussion there or anywhere else in the description, however, of yeast cells being used for expression of polypeptides. The only type of host cells identified as being used for expression in the written description of the '545 patent are bacterial host cells. Altman Declaration, ¶ 12; McKnight Declaration, ¶ 12. As such, the Office is incorrect in stating that the Moore '545 written description describes eukaryotic cells, such as yeast, which produce and secrete functioning rFv. 5/21/07 response: pp.19-20.

Examiner Response: The Examiner respectfully disagrees.

The *Moore* document, taken as a whole, clearly discloses and enables the concept of using both non-secreting prokaryotes, such as bacteria, as well as secreting eukaryotes, such as yeast, for expression of antibody chains. Although, *Moore* defines an "appropriate host" for expression in the context of the amplification step (at col. 5, lines 47-52) to include both *E.Coli.* and yeast it is equally clear that *Moore* encompasses yeast as an "appropriate host", by the nature of its ability to express and secrete antibody chains. This is clearly supported by the *Moore* patent disclosure at columns 8-10 which details two expression host strategies, in which one expression host secretes polypeptide e.g, yeast, while another expression host is a non-secretor e.g. *E.Coli* that requires lysing the host in order to recover the expressed antibody polypeptide for reconstituting rFv. See especially col. 8, lines 1-11; col. 10, lines 22-60.

The Cabilly Patented Inventions:

i. The Instant 6,331,415 (Cabilly 2) Patented Invention Undergoing Reexamination

The following patent claim methods and compositions are representative:

METHODS:

1. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell comprising:

(i) transforming said single host cell with a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a second DNA sequence encoding at least the variable domain of the immunoglobulin light chain, and
(ii) independently expressing said first DNA sequence and said second DNA sequence so that said immunoglobulin heavy and light chains are produced as separate molecules in said transformed single host cell. See Claim 1.

33. A process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell comprising: independently expressing a first DNA sequence encoding at least the variable domain of the immunoglobulin heavy chain and a. second DNA sequence encoding at least the variable domain of the immunoglobulin light chain so that said immunoglobulin heavy and light chains are produced as separate molecules in said single host cell transformed with said first and second DNA sequences.

21. A method comprising:
a) preparing a DNA sequence consisting essentially of DNA encoding an immunoglobulin consisting of an immunoglobulin heavy chain and light chain or Fab region, said immunoglobulin having specificity for a particular known antigen;
b) inserting the DNA sequence of step a) into a replicable expression vector operably linked to a suitable promoter;
c) transforming a prokaryotic or eukaryotic microbial host cell culture with the vector of step b);
d) culturing the host cell; and
e) recovering the immunoglobulin from the host cell culture, said immunoglobulin being capable of binding to a known antigen.

COMPOSITIONS:

15. A vector comprising a DNA encoding at least a (first) variable immunoglobulin heavy chain domain and a second DNA sequence encoding at least a variable immunoglobulin light chain domain wherein the 1st and 2nd DNA sequences are located at different insertion sites in the vector.

18. A transformed host cell comprising at least two vectors in which one vector comprises a variable immunoglobulin heavy chain domain and a second vector comprises a variable immunoglobulin light chain domain.

32. The insoluble particles of heavy and light chains or Fab region produced by the method of claim 21 in which the heavy and light chains or Fab regions are deposited within the cells (e.g. claim 27).

ii. The Reference US Pat. No. 4,816,567 Cabilly 1 Patent Claims:

Independent claims 1, 3, 5, and 7 of the '567 patent read as follows;

1. A method comprising
a) preparing a DNA sequence encoding a chimeric immununoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;
b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;
c) transforming the host cell with the vector of (b);
d) culturing the host cell; and
e) recovering the chimeric heavy or light chain from the host cell culture.

3. A composition comprising a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a
second, different mammalian species.

5. A replicable expression vector comprising DNA operably linked to a promoter compatible with a suitable host cell, said DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen and having a constant region homologous to a corresponding region of an antibody of a first
mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

7. Recombinant host cells transformed with the vector of claim 5.

Claims 2, 4 and 6 (dependent on claims 1, 3 and 5, respectively) recite that the first mammalian species (i.e. the source of the constant region) is human.

Cabilly 1 ('567 Patent) and Cabilly 2 ('415 Patent) Claim Interpretation

Antibodies are proteins that generally refer to tetramers or aggregates thereof having specific immunoreactive activity comprising light and heavy chains in a "Y" configuration (having variable branch and constant stem regions), with or without covalent linkage. '567 patent col. 6, lines 14-18.

Similarly, an "immunoglobulin" generally comprises two heavy and two light chains "but may have specific immunoreactive activity (i.e. an "antibody") or lack such

specific immunoreactive activity (i.e. "non-specific immunoglobulin" or "NSI"). See Cabilly I patent col. 6, lines 18-20; and Cabilly 2 patent Fig. 1.

The phrase "chimeric immunoglobulin heavy or light chain" refers to a species of immunoglobulin heavy or light chain in which the constant region is homologous to the constant region of an antibody of a first mammalian species and the variable region is homologous to the variable region of an antibody derived from a second, different mammalian species. See claim 1 and 3 definition;'567 patent col. 6, lines 48-59.

The phrase "replicable expression vector (comprising DNA) operably linked to a suitable promoter compatible with a host cell" of Cabilly 1 claims 1 and 5 is discussed in the '567 patent specification. An "expression vector" includes:

> ... vectors which are capable of expressing DNA sequences contained therein, i.e., the coding sequences are operably linked to other sequences capable of effecting their expression. It is implied, although not always explicitly stated, that these expression vectors must be replicable in the host organisms . . . . '567 patent, col. 8, 11. 21-27.

"Host cells," in Cabilly 1 claims 1 and 7, include prokaryotic or eukaryotic cells, such as eukaryotic microbes, and cells derived from multicellular organisms, like mammalian cells. See '567 patent, col. 8, line 46 to col. 10, 1ines 13-30, 57 .

The light or heavy chain Cabilly 1 claim 1 recovery step encompasses " ...methods known in the art, but the choice of which is necessarily dependent on the form in which the protein is expressed. " '567 patent, col. 13, lines 3-6.

The recombinant procedures used to obtain the DNA sequences, prepare vectors, transform cells, culture cells, and recover the immunoglobulins are the same, whether for recombinant immunoglobulins that mimic naturally occurring ones or for altered recombinant immunoglobulins, such as chimeric antibodies. See e.g., '567 patent, col. 15, lines 59 to col. 16, line 15; and col. 28, lines 44-47.

OUTSTANDING DOUBLE PATENTING REJECTION:

7. Claims 1-36 of U.S. Pat. No. 6,331,415 (Cabilly 2) are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 4,816,567 (Cabilly 1) in view of Axel et al. U.S. Pat. No. 4,399,216 (8/83), Rice and Baltimore, PNAS USA 79 (12/82):7862-7865, Kaplan et al. EP 004722 (1/82), Builder et al. U.S. Pat. No. 4,511,502 (issued 4/85), Accolla et al. PNAS USA 77(1): 563-566 (1980), Dallas (WO 82/03088), Deacon (Biochemical. Society Transactions, 4 (1976):818-820), 1981 Valle (Nature, 291 (May '81) pages 338-340; Ochi (Nature, 302 (3/24/83) pages 340-342 alone, or further in view of Moore et al. U.S. Pat. No. 5,840,545 (Nov. 24, 1998: effectively filed March 15, 1982).

The Reference Cabilly 1 Patent Claims:

It is noted that this double patenting rejection utilizes the Moore '545 patent for its teaching of single chain antibody expression in separate hosts along with the reconstitution of assembled active antibody.

The Cabilly 1 invention is drawn to:

Claim 1. A method comprising

a) preparing a DNA sequence encoding a chimeric immununoglobulin heavy or light chain having specificity for a particular known antigen wherein a constant region is homologous to the corresponding constant region of an antibody of a first
mammalian species and a variable region thereof is homologous to the variable region of an antibody derived from a second, different mammalian species;
b) inserting the sequence into a replicable expression vector operably linked to a suitable promoter compatible with a host cell;
c) transforming the host cell with the vector of (b);
d) culturing the host cell; and
e) recovering the chimeric heavy or light chain from the host cell culture.

Claim 3. A composition comprising a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen having a constant region homologous to a corresponding constant region of an antibody of a first mammalian species and a variable region homologous to a variable region of an antibody derived from a
second, different mammalian species.

Claim 5. A replicable expression vector comprising DNA operably linked to a promoter compatible with a suitable host cell, said DNA encoding a chimeric immunoglobulin heavy or light chain having specificity for a particular known antigen and having a constant region homologous to a corresponding region of an antibody of a first
mammalian species and a variable region homologous to a variable region of an antibody derived from a second, different mammalian species.

Claim 7. Recombinant host cells transformed with the vector of claim 5.

Claims 2, 4 and 6 (dependent on claims 1, 3 and 5, respectively) recite that the first mammalian species (i.e. the source of the constant region) is human.

In the reference *Cabilly 1* disclosure, "immunoglobulins" are defined as being comprised of light (kappa or lambda) and heavy chains (gamma, mu, alpha, delta or epsilon), which when assembled, possess "specific immunoreactive activity" and are labeled "antibodies". See *Cabilly 1* at col. 3, lines 15-42; col. 6, lines 14-24.

The reference *Cabilly 1* defines the phrase "chimeric immunoglobulin heavy or light chain" as referring to a species of immunoglobulin heavy or light chain in which the constant region is homologous to the constant region of an antibody of a first mammalian species and the variable region is homologous to the variable region of an antibody derived from a second, different mammalian species. See Cabilly 1 patent: col. 6, lines 48-59.

The reference *Cabilly I* patent includes mammalian chimeric immunoglobulin light and heavy chains which are derived from humans (dependent claims 2 and 4). Mammalian antibody sources are derived in situ from mammalian B lymphocytes or from cell culture hybridomas. See *Cabilly 1* patent col. 1, lines 38-42.

The reference *Cabilly 1* claimed "(replicable) expression vector" is defined as vectors capable of expressing DNA sequences contained therein which are frequently in the form of plasmids, thus 'plasmid' and 'expression vector' are often used interchangeably. See *Cabilly* 1 patent col. 8, lines 21-45.

The reference *Cabilly 1* claimed "host cells" include prokaryotic (most preferably the gram (-) bacteria E. Coli. Strains ATCC: 31446 and 31537) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See *Cabilly 1* patent , col. 8, 1ine 46 to col. 10, lines 13-30, 57.

The reference *Cabilly 1* claimed means of successfully "recovering the chimeric heavy or light chain from the host cell culture" (above claim 1 step e) is determined by the type of protein and host organism but utilizes art known techniques including cell lysis of insolubilized particles present in the host (e.g. gram-negative E. Coli) followed by denaturant solubilization unless the host organism normally secretes the protein out of the cell (e.g. some yeast and gram positive bacteria). See Cabilly 1 patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Both the *Cabilly 1* and the instant *Cabilly 2* patented inventions include claims directed to the same statutory subject matter: recombinant processes, vectors and host cells for making immunoglobulins (particularly chimeric immunoglobulins) and immunoglobulin products. The recombinant procedures used to obtain the DNA sequences, prepare vectors, transform cells, culture cells, and recover the immunoglobulins are the same, whether for recombinant immunoglobulins that mimic naturally occurring ones or for altered recombinant immunoglobulins, such as chimeric antibodies. See e.g., '567 patent, col. 15, lines 59 to col. 16, line 15; and col. 28, lines 44-47.

The reference *Cabilly 1* patent specification discloses expressing heavy and light chains preferably for immunoglobulin assembly, a utility which is supported by the reference *Cabilly 1* claimed antigen specificity of its chains; and thus it is appropriate to construe the reference *Cabilly 1* patent claims to suggest production of chimeric immunoglobuins (e.g. antibodies) using recombinant technology, and vectors and host cells for doing so. *Geneva Pharmaceuticals, Inc.*, 349 F.3d at 1385, 68 USPQ 2d at 1875.

The instant *Cabilly 2* patented generic invention drawn to producing an immunoglobulin (or immunologically active fragment) clearly encompasses the chimeric immunoglobulin species (or immunologically active fragment) as evidenced by instant patent claim13 encompassing a chimeric immunoglobulin.

The reference *Cabilly 1* patented invention differs from the instant patent since it fails to teach the co-expression of light and heavy antibody chains in a host cell.

i. One of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference Cabilly 1 patented invention in light of the prior art

Axel teaches a process for inserting foreign DNA into eukaryotic cells by co-transforming the cells with the disclosed foreign DNA and an unlinked DNA that codes for a selectable phenotype not otherwise expressed by the cell (see col. 3, lines 21-27). *Axel* describes the process as particularly suited for the transformation of DNA into eukaryotic cells for making antibodies (see col. 3, lines 31-36). *Axel* discloses and claims the expression of antibodies in mammalian host cells as intact (assembled)

proteins. See *Axel:* abstract; col. 5, lines 3-7 and 24-28; patent claims 1, 7, 22-24, 28 and 29.

Rice introduced a recombinant rearranged murine kappa light chain gene construct into an Abelson murine leukemia virus (A-MuLv)-transformed lymphoid cell line which already synthesized y2b heavy chain protein (see page 7862). Rice inserted the light chain gene into a plasmid, transfected the cells, and then examined the polypeptides as well as the RNA produced by the cells (see pages 7863-7864 and Figures 2 and 3). Lastly, since the cells were producing both immunoglobulin light and heavy chains, the cells were examined for the ability to assemble the chains into IgG molecules, leading to the observation that "[e]ssentially all of the k chain produced in the K-2 cells appear to be assembled into IgG2b" (see page 7864 and Abstract penultimate sentence). Thus, *Rice* demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins.

Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains to specific antigens. By using known molecular biology techniques, the mRNA's can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see page 3, lines 4-9).

In addition, *Kaplan* teaches that a variety of host cells (e.g. bacteria and yeast) and plasmids (particularly pBR322) may be used to express recombinant heavy and light chains (see page 10, lines 1-33).

Dallas teaches that two different proteins (in addition to a selectable marker) can be expressed in a single cell and such expression may be accomplished by the use of two vectors, each containing DNA encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins. (See Example IV, as well as page 8, lines 9-11, which disclose the use of a single vector, and page 9, lines 27-29, which discloses the use of two vectors). More particularly, a plasmid containing a HindIII DNA fragment encoding one protein was subcloned into a separate site of a second plasmid containing a BamHI DNA fragment encoding a second protein to form a

single plasmid used for independently expressing both proteins in a single cell. See page 8, lines 11-17 and page 7, lines 29-33.

Thus, the *Axel, Rice and Kaplan* references taken in view of the *Dallas* reference teaching would provide motivation to one of ordinary skill in the art at the time the instant invention was made to modify the *Cabilly 1* patented invention to transform a single host with

a. the individual *Cabilly 1* vectors separately containing a light or heavy chain; or

b. a modified *Cabilly 1* vector encoding both an immunoglobulin light and heavy chain for independent expression of these chains.

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant invention was made to modify the *Cabilly 1* patented invention so as to co-transform a single host with two vectors each containing DNA encoding a light or heavy chain, or to utilize a single vector containing both light and heavy chain DNA in order to transform a host cell to independently express said DNA sequences as in *Cabilly 2* patent claims 1, 15, 18, 21 and 33 (and claims dependent thereon).

ii. The prior art provides further motivation to make active antibody with a reasonable expectation of success.

The *Deacon* and *1981 Valle* references introduced and expressed exogenous light and heavy chains into eukaryotic cells achieving assembled functional immunoglobulins.

Additionally, the *Ochi* reference restored specific antibody production by cloning light immunoglobulin chain into a cell line endogenously producing heavy immunoglobulin chain.

More specifically, *Deacon* teaches injecting mRNA encoding heavy and light immunoglobulins (to hemocyanin or ferritin antigen) into Xenopus (frog) oocytes (see Abstract; and page 818 for procedure) and concludes (page 829, lines 1-5) that "mRNA from hyperimmunized rats, when injected into oocytes, is translated into heavy and light chains" and that "in oocytes, heavy and light chains can be assembled into immunoglobulin molecules, which can behave as antibodies directed against antigen".

Similarly, *1981 Valle* taught that microinjection of mRNA encoding light (kappa) and heavy (gamma 1) chains from immunoglobulin MOPC21 (produced by mouse plasmacytoma P3/X63 cell line) into Xenopus oocytes resulted in oocyte assembly and secretion of tetrameric mouse immunoglobulin upon addition of horse serum to the oocyte medium to prevent "gratuitous oxidation". See Valle Abstract, page 338, col. 2; page 339, col. 2; and Figure 2B, Track 4 showing secreted tetrameric antibody.

Although the above-discussed *Deacon and 1981 Valle* references utilize m-RNA, as compared to the use of vector DNA in the *Cabilly 1* claims for encoding the corresponding light and heavy immunoglobulin chains, once the m-RNA or vector DNA is expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression. Accordingly, the difference between using vector DNA vs. mRNA for host transformation is not substantive.

Additionally, *Ochi* discloses that an exogenous light immunoglobulin chain specific for 2,4,6-trinitrophenyl (TNP) cloned into a mammalian cell (mutant igk-14 producing heavy chain specific for TNP but not light chain) results in the cell's assembly and secretion of a functional immunoglobulin (i.e. binds TNP). See Abstract; Figures 1 and 2; last full paragraph on page 340; and Table 1).

Accordingly, the *Deacon, 1981 Valle and Ochi* references taken separately or in combination provide further motivation to perform the Cabilly 1 patented steps in a single host cell for producing a chimeric heavy and light chain which is assembled into active antibody thus rendering obvious the production of a functional immunoglobulin with a reasonable expectation of success to one of ordinary skill in the art at the time the instant invention was made.

Additionally, the *Moore patent* reference provides further motivation to express, using two vectors, the Cabilly 1 patented light and heavy antibody chains comprising variable regions in separate prokaryotic (E. Coli) or eukaryotic (yeast) host cells with a reasonable expectation of producing an assembled functional single-chain antibody.

Moore disclose and claim a hybrid DNA strategy for the preparation of specific binding polypeptides comprised of two different polypeptide chains, which together assume a conformation having high binding affinity to a predetermined ligand

or haptenic site thereof (see e.g. Moore '545, col. 2, lines 39-52). One or both of the different polypeptide chains derived from the variable region of the light and heavy chains of an immunoglobulin may be used to provide specific binding analogous to the binding site of an immunoglobulin, with the composition being referred to as an "rFv" and with the portions corresponding to L-rFv (variable light region of an antibody)and H-rFv (variable heavy region of an antibody), thus forming a functioning single chain antibody (compare to instant patent "Fab proteins" or "univalent antibodies" Cabilly '415 patent col. 5, lines 17-28).

Accordingly, the *Moore patent* discloses a method of making an "immunologically functional immunoglobulin fragment" comprising independently expressing in a host variable heavy and light chain domains e.g. rFV including heavy chain gamma and light chain kappa lacking constant regions as in instant claims 23-25. See Moore col. 1, lines 33-42; col: 3, lines 59-63; col. 17, lines 4-8). Additionally, Moore teaches a prokaryotic (E.Coli) or eukaryotic (yeast) transformed "host cell". See Moore at col. 5, line 48 to top of col. 6; col. 7, lines 39-50 with pBR322 vector; col. 8, lines 1-16. col: 10, lines 1-5; col. 23, lines 35-45 (pBR322); and col. 24, lines 50-60 (pGM1L and pGM1H); col. 11, lines 5-12] thus addressing the single chain embodiments of claims 1-7, 10, 14 and 23-25.

***Obviousness of Dependent Claims* 5-10, 12, 14, 19-20, 22, 26-32 and 34-36**

The Cabilly 1 patent claims render obvious dependent claims 5-10, 12, 14, 19-20, 22, 26-32 and 34-36 for the following reasons.

The Cabilly 1 patented invention teaching differs from the instant claims by:

a. using vector plasmid pBR322 (claim 5);
b. using bacterial/yeast/mammalian host cells including E Coli strain X1776 (claims 6-8, 19, 20, and 26);
c. secretion from transformed host (e.g. mammalian) of a functional immunoglobulin (claims 9 and 29);
d. insolubilized antibody in the transformed host (e.g. E.Coli) which is solubilized and refolded to form functional immunoglobulin (claims 10 and 27-32)
e. same source for DNA of constant and variable domains (claim 12)
f. mononclonal DNA source of constant and variable domains (claim 14)
g. transforming an anti-CEA antibody (claim 22); and
h. attaching drug or label to the immunoglobulin molecule (claims 34-36).

a. Instant claim 5 is obvious

As discussed *supra*, the *Cabilly 1* claimed "(replicable) expression vector" is interchangeable with "plasmid" due to the frequent use of these vectors. Axel (col. 8, lines 7-35) and Kaplan (page 10) teach using plasmids, particularly pBR322, for expressing heterologous proteins thus rendering the use of this particular plasmid species obvious for use in the *Cabilly 1* patented recombinant methods.

b. Instant claims 6-8, 19, 20 and 26 are obvious

Instant claim 6 recites that the host cell is a bacterium or yeast.
Instant claim 7 recites a host cell is E. coli (a bacterium) or S. cerevisiae (a yeast),
Instant claim 8 recites that the bacterial host cell is E. coli strain X1776.
Instant claims19 and 20 recite mammalian host cells.
Instant claim 26 recites that the host cell is E. coli or yeast.

Each of these host cells is a host cell within the scope of claim 1 of the reference Cabilly 1 patent.

Additionally, *Axel* teaches mammalian host cells for expressing proteins, particularly antibodies. *Axel,* col. 5, lines 3-7 and 24-28.

Rice demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell. Rice, p. 7863. Kaplan teaches bacteria and yeast host cells for expressing recombinant immunoglobulin chains (Kaplan, p.10, lines 1-33). Thus, the instant Cabilly 2 patent claims 6-8, 19, and 26 are obvious variants of the reference Cabilly 1 patent claims.

c. Instant claims 9 and 29 are obvious

Instant claims 9 and 29 are drawn to expression and secretion of an immunologically functional immunoglobulin.

The reference *Cabilly 1* patent claims encompass expressing immunoglobulin proteins in host cells that are capable of secreting immunologically functional immunoglobulins. *Cabilly 1* "host cells" include prokaryotic (most preferably the bacteria E. Coli.) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See Cabilly 1 patent, col. 8, 1ine 46

to col. 10, lines 13-30, 57. In this regard, the *Cabilly 1* patent claims encompass recovery of chimeric light or heavy chains by:

a. cell lysis of insolubilized particles present in the host followed by denaturant solubilization; or

b. host cell secretion of active protein.

See *Cabilly 1* patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Axel teaches mammalian host cells for expressing heterologous proteins, including antibodies. See Axel: abstract; col. 5, lines 3-7 and 24-28; patent claims 1, 7, 22-24, 28 and 29. *Rice* demonstrates expression of a recombinant immunoglobulin light chain in a mammalian host cell (*Rice* p.7863). Thus, the selection of host cells capable of secreting proteins for use in the *Cabilly 1* patented invention would have represented an obvious design choice in view of the Axel and/or Rice references.

d. Instant claims 10 and 27-32 are obvious

Instant claims 10 & 27-32 are drawn to expressing insolubilized antibody in the transformed host (e.g. E.Coli) that is solubilized and refolded to form immunoglobulin.

The *Cabilly 1* patent claims encompass expressing immunoglobulin proteins in host cells (e.g. E. Coli) in insoluble form which is then solubilized and refolded to form functional immunoglobulin. *Cabilly 1* "Host cells" include prokaryotic (most preferably the bacteria *E. Coli.*) or eukaryotic cells, including eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See '567 patent, col. 8, 1ine 46 to col. 10, lines 13-30, 57. In this regard, the Cabilly patent claims encompass recovery of chimeric light or heavy chains by:

a. cell lysis of insolubilized particles present in the host followed by denaturant solubilization; or

b. host cell secretion of active protein.

See *Cabilly 1* patent col. 4, lines 27-35; col. 12, line 66-col. 13, line 18.

Kaplan teaches bacteria and yeast cells for expressing recombinant immunoglobulin chains (p. 10, lines 1-27) and Kaplan also describes rupturing the host cells, isolating the heavy and light chains and combining them under mildly oxidative

conditions to promote refolding and disulfide bond formation. See Kaplan at page 10, lines 1-33.

Similarly, *Builder et al.* teach expression of exogenous or foreign proteins in host cells (e.g. bacteria) in insoluble form that is recovered, solubilized and refolded. See Kaplan columns 2-6 and Schemes 1 and 2.

Thus, the instant patent claims 10 and 27-32 are obvious variants of the reference *Cabilly 1* patent claims in view of *Kaplan* and/or *Builder*.

e. Instant claim 12 is obvious

Claim 12 of the instant patent requires that the constant and variable domains be derived from the same source of DNA.

Although the reference *Cabilly 1* patent is directed to utilizing DNA encoding heavy or light chains from different sources (e.g. chimeric), it would have been obvious to utilize heavy or light chain DNA from the same source in light of the use of same source DNA as taught by both the Kaplan (e.g. from human hybridomas) and/or the *Rice* reference (e.g. from mice), especially since non-chimeric expression was conventional in the art.

f. Instant claim 14 is obvious

Claim 14 of the instant patent requires that the constant and variable domains be derived from one or more monoclonal antibody producing hybridomas.

Kaplan teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains (including variable and constant domains) to specific antigens. By using known biology techniques, the mRNAs can be used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see *Kaplan* p. 3, lines 4-9). In addition, Kaplan teaches that a variety of host cells (e.g. bacteria and yeast), may be used to express such recombinant immunoglobulin heavy and light chains (see page 10, lines 1-33). Accordingly, employing monoclonal antibodies as a source of DNA encoding heavy and light chains (variable and constant domains) would have been obvious in light of the *Kaplan* teaching.

g. Instant claim 22 is obvious

Claim 22 of the instant patent limits the method of claim 21 to making an anti-CEA (i.e. an antibody to carcinoembryonic antigen).

CEA is an antigen within the general scope of a "particular known antigen" of the reference *Cabilly 1* patent claim 1. Additionally, the instant *Cabilly 2* patentee admits that anti-CEA antibodies are useful for tumor detection and perhaps useful in treating tumors that have CEA receptors at their surface. See *Cabilly 2* patent, col. 16, lines 31-38 and references cited therein.

Additionally, *Accola et al.* describes making anti-CEA monoclonal antibodies.

Accordingly, instant claim 22 represents an obvious variant of the reference *Cabilly 1* patented invention in light of the reference *Cabilly 1* patented claimed teaching and the art-recognized motivation to make claim 22 CEA antibodies for diagnostic or therapeutic purposes.

h. Instant claims 34-36 are obvious

Claims 34-36 (dependent on 9, 10 and 33) further include attaching a label or drug to the immunoglobulin.

Kaplan (page 8, lines 7-21) teaches the use of antibodies for site directed therapy (i.e. via drug attachment) or diagnostic use (i.e. via label attachment for localization).

Accordingly, it would have been obvious to modify the reference *Cabilly 1* claimed antibodies to attach a drug and/or label for use in therapy and/or diagnostics, respectively.

Patent Owner's Responses (1/25/05; 10/30/06 and 5/21/07) And Examiner Rebuttal:

1. Patent owner argues that the findings of the PTO during prosecution of the '415, '567 and Boss Patents establish that the instant Cabilly 2 ('415) patent claims are patentably distinct from the claims of the reference Cabilly 1 ('567) patent. The Patent Owner cites the Board's failure to introduce the Cabilly 1 patent claims into the interference between the Cabilly 2 (copied) claims and the Boss patent claims; and additionally an interview conducted on October 4, 2001 during the Cabilly 2 patent prosecution indicating the failure of the Examiner to raise double patenting between the Cabilly 1 and 2 patent claims. See also 5/21/07 response page 17, footnote 6.

Examiner Response:

These arguments were considered but not deemed persuasive.

Initially, it is noted that 35 U.S.C. 121 does not preclude obviousness double patenting. See 90/007,542 August 16, 2006 office action at pages 5-6 herein incorporated by reference. Additionally, the above argument is not persuasive since a rejection resulting from a substantial new questions of patentability is now based on references (or combination of references) which were not considered and/or appreciated by the Examiner in the earlier concluded examination(s) nor by the Board judges in the interference proceeding. MPEP 2258.01.

2. Office incorrectly states that the '567 patent includes claims directed to the same subject statutory subject matter as the '415 patent, including "recombinant processes, vectors and host cells for making immunoglobulins and immunoglobulins products." See: 2/07 Office Action, pp.18, 28; 5/21/07 Owner Response, p.30.

Examiner Response:

Patent owner's argument is misguided.

The complete context from which the above quoted subject matter was taken is as follows:

> Both the Cabilly 1 and the instant Cabilly 2 patented inventions include claims directed to the same statutory subject matter: recombinant processes, vectors and host cells for making immunoglobulins (particularly chimeric immunoglobulins) and immuno-globulin products.

In the above phrase, "immuno-globulin products" refer to immunoglobulin chains of the *Cabilly 1 patent*, whereas immunoglobulins refer to the instant Cabilly 2 patented invention. In any event, it is clear that both patented inventions are directed to *analogous statutory subject matter, e.g.,* recombinant process, vectors and host cells.

3. Cabilly 1 patent claims can only be used for definitional purposes to interpret the meaning of an unclear claim term or element. In order "[T]o advance its obviousness-type double patenting conclusions, the Office improperly reads unclaimed elements into the '567 claims and impermissibly draws from the teachings in the common patent disclosure shared by the '567 and '415 patents. Cabilly 1 disclosure regarding utility is not prior art knowledge available for purposes of motivation. Part of the Office's error stems from the way it has read the clause "having specificity for a particular known antigen" in the '567 patent claims, based on suggestions that it found in the specification". Dr. Harris's declaration opines that the phrase "having specificity for a particular known antigen" in the Cabilly 1 patent "does not mean that the individual chimeric immunoglobulin chain must exhibit-by itself-antigen binding functionality, or that the chimeric chain must be incorporated into an immunoglobulin molecule or immunologically functional fragment. Dr. Riggs' declaration opines that separate recombinant production of immunoglobulin light or heavy chains was useful to raise monospecific antisera for diagnostic use, such as to clinically diagnose and monitor multiple myeloma. Thus, the rejection improperly incorporates a disclosed utility into the Cabilly 1 patented invention for providing motivation to make an antibody. The rejection's use of the Geneva case is distinguished as a holding regarding a single disclosed utility. See 2/07 Office Action, pp. 16, 18, 29; 5/21/07 response pp.30-38.

Examiner Response:

These arguments were considered but not deemed persuasive.

Initially, it is pointed out that the above obviousness rejection provides various reference teachings, in addition to the Cabilly I patented invention, to provide motivation to assemble an antibody.

In any event, the following phrase present in the obviousness rejection is currently at issue:

> "The reference Cabilly 1 patent specification discloses expressing heavy and light chains preferably for immunoglobulin assembly, a utility which is supported by the reference Cabilly 1 claimed antigen specificity of its chains; and thus it is appropriate to construe the reference Cabilly 1 patent claims to suggest production of chimeric immunoglobuins (e.g. antibodies) using recombinant technology, and vectors and host cells for doing so. *Geneva Pharmaceuticals*, Inc., 349 F.3d at 1385, 68 U.S.P.Q. 2d at 1875".

As pointed out in the rejection, the Cabilly 1 patented method clearly addresses the recombinant making of a heavy or light chain "**having specificity for a particular known antigen**" which comprises "a variable region thereof" which "is homologous to the variable region of **an antibody** derived from a second, different mammalian species" (emphasis provided).

In this context the rejection states that one of ordinary skill in the art would " ...construe the reference Cabilly 1 patented claims to suggest production of chimeric immunoglobulins (e.g. antibodies) using recombinant technology". In other words, the Cabilly 1 patent claims teach the recombinant method of making light and heavy chains which would motivate one of ordinary skill in the art to make an antibody or antibody fragment.

As further pointed out in the rejection, this finding was entirely consistent with the Cabilly 1 patented disclosure's definition of producing an antibody (a preferred utility) defined as an assembled immunoglobulin that binds antigen. Assembly entails either covalently linking light and heavy chains via disulfide bonds or non-covalently associating these chains in the correct geometry for antigen binding. Even those immunoglobulins which lack the specificity of antibodies are useful, "although over a smaller spectrum of potential uses", such as "in protein replacement therapy for globulin related anemia ...". See Cabilly I Background Discussion admissions at col. 3, lines 1-14 and lines 34-42.

Thus, it is the Cabilly 1 patented invention, as interpreted by one of ordinary skill in the art in light of the state of the prior art, and not the specification, that provides the teaching or suggestion of assembling an antibody.

The rejection is consistent with the *Geneva Pharmaceuticals Inc.* case.

In *Geneva Pharmaceuticals* the CAFC deemed it necessary to "examine(s) the specifications of both patents to ascertain any overlap in the claim scope for the double patenting comparison" citing *In re Avery* and *In re Zickndraht*. See *Geneva Pharmaceuticals, Inc.*, 349 F.3d at 1385, 68 U.S.P.Q. 2d at 1875 case citations provided therein. Although the prior patented composition provided only physical compound characteristics, consideration of the underlying specification by the CAFC

revealed the disclosure of only a single utility which was subsequently claimed in the second patent.

The present rationale for consulting the underlying *Cabilly 1* specification for determining possible overlap of the *Cabilly 1 and 2* invention is more compelling than that found in the *Geneva* case, since unlike *Geneva*, the *Cabilly 1* patented claims *suggest* antibody assembly, a preferred utility which is supported by the underlying specification definition of an "antibody".

Additionally, the specification can be used in the context of a double patenting rejection as a dictionary to learn the meaning of a term in the patent claim. *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999) ("[W]ords in patent claims are given their ordinary meaning in the usage of the field of the invention, unless the text of the patent makes clear that a word was used with a special meaning."). Accordingly, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in a different application or patent defines *an obvious variation*. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970).

In attempting to clarify the meaning of the phrase "having specificity for a particular known antigen", the patent owner refers to the definition of the term "chimeric" as it refers to "chimeric antibodies" i.e. light or heavy antibody chains in which the variable and heavy chains are derived from different species. Further, as argued by the owner, the 1st Dr. Harris Declaration defines the same phrase as referring to deriving "from the variable domains of an antibody or an antibody fragment exhibiting an antigen binding function". See 90/007,542 proceeding; 10/30/06 owner response pages 22-23.

In an analogous manner, in order to define the phrase "having specificity for a particular known antigen", the examiner pointed to the reference Cabilly 1 patent (col. 1, lines 30-35; and col. 1, lines 14-23) that describes two types of immunoglobulins:

a. non-specific immunoglobulins which lack antigen specificity and are "produced at low levels by the lymph system and in increased levels by myelomas" (emphasis); and

b. immunoglobulins containing assemblies of light and heavy chains which have specific immunoreactive activity.

In light of the Cabilly 1 patent's claimed teaching of the ability to separately make light and heavy chains each of which possess: variable regions "having specificity for a particular known antigen" which are "homologous to the variable region of an antibody", it is reasonable to one of ordinary skill in the art to interpret the Cabilly 1 patented invention as suggesting the use of the Cabilly 1 claimed immunoglobulin chains for assembly into antibodies, in contradistinction to an alternative less preferred use, e.g., in diagnosing myeloma.

This interpretation is additionally supported by the fact that the Cabilly 1 claims encompass the making of an antibody as the most preferred utility. It is also supported by the Cabilly 1 specification definition of an "immunoglobulin" and by the patent owner's own argument defining the term "chimeric heavy or light chain" by reference to the definition of a "chimeric antibody". Accordingly, the Examiner is not improperly importing specification utilities into the claims or relying on the specification for motivation as asserted by the patent owner.

4. It is asserted that the Office erred in concluding that the "Cabilly 1 patented method is part of the state of the prior art as of 1983", with the owner relying on the General Food Corps case (and citations cited therein) for support. See Feb. 2007 Office Action, p. 45; Owner 5/21/07 response p.31.

Examiner Response:

This argument is not found persuasive.

In the rejection, after comparing the similarities in scope between the Cabilly 1 and 2 patented inventions regarding subject matter, the following rejection statement is now at issue:

> "Accordingly, the Cabilly 1 patented method as directed to the making of vectors (e.g.cDNA) encoding mammalian light and heavy chains and their expression separately in host cells, including prokaryotic and eukaryotic host cells, is part of the state of the prior art as of 1983".

The case law cited by the patent owner in support of their argument is directed to facts faced by the CAFC in the *General Food Corps* case that are inapplicable to the present instance.

In *General Foods*, the CAFC faced a rationale for obviousness double patenting where the "principle error" was the lower court focusing their inquiry on a single step (step 1a) of a prior '619 patented method where the method included 9 steps:

> "This concept violates the fundamental rule of claim construction, that what is claimed is what is defined by the claim *taken as a whole*, every claim limitation (here each step) being material. What is patented by claim 1 of '619 is a 9- step caffeine recovery process, nothing more and nothing less". *General Food Corps,* 972 F.2d at 1280, 23 U.S.P.Q. 2d at 1845 (with emphasis).

Accordingly, the CAFC in *General Foods* found that:

> "[A] further error of the trial court in dealing with the '619 patent's claim 1 was in looking, not at what invention it defines, but at whatever the claim discloses... [W]e repeat, clause (a) of claim 1 is not a claim, patent '619 does not claim clause (a) but a 9-step process of which (a) is the first step, and double patenting is based entirely on what is claimed, reading each claim as an entirety to determine what invention it defines". *General Food Corps,* 972 F.2d at 1281, 23 U.S.P.Q. 2d at 1846.

Contrary to the claim construction error addressed in *General Foods*, the instant rejection is not improperly focusing on a single method step but is properly focusing on the teaching of the patented *Cabilly I* method invention *taken as whole* to one of ordinary skill In the art.

5. Obviousness rejection fails to address three differences between the '415 Cabilly 2 and the '567 Cabilly 1 patent:

a. single host transformed with two sequences;
b. production of heavy and light chains as separate molecules in the transformed host;
c. assembly of the heavy and light chains.

Owner 11/25/05 Response pp. 24-25, 28-29, 31, and Tables 2-6 of Exhibit E; Owner 10/30/06 Response pp. 16-17, 29-30; Owner 5/21/07 response pp. 28-29.

Examiner Response:

This argument is not persuasive.

The rejection clearly addresses the critical distinction of co-expressing the light and heavy chain together in a single transformed host.

As further discussed in the rejection, none of the references of record teach or suggest expressing the light and heavy chains as a fusion protein as implied by the patentee since utilizing this construct would make assembly of the light and heavy chains prohibitive. In fact, the prior art references of record clearly teach the independent expression of separate proteins in all host systems. See e.g. *Axel* for separate expression of heterologous proteins in a single eukaryotic host; *Dallas* teaching of the separate expression of bacterial proteins in a single bacterial host; and *Rice*, *Deacon*, *Valle, Oi* and *Ochi* for independent expression in secreting mammalian hosts.

Although assembly is not affirmatively claimed, the rejection nevertheless clearly addresses the assembly of both immunoglobulins and fragments thereof upon recovery e.g. by lysis or secretion. See independent Cabilly 2 patent claims 1, 21 and 33.

6. Axel does not suggest processes for producing and isolating multiple different polypeptides from a transformed host cell but only a single protein (encoded by DNA I) and a selectable marker (encoded by DNA II). The Axel reference although mentioning "antibodies" as an exemplified polypeptide, fails to disclose procedures for producing immunoglobulin molecules or immunologically functional fragments having both heavy and light chains. Accordingly, where DNA I is drawn to an antibody, this should be interpreted to be a light or heavy chain but not assembled antibody tetramers. A person of ordinary skill in the art, in early 1983, would not have read the passing references in Axel to "antibodies" as indicating that antibody heavy and light chains should be co-expressed in one host cell. The Axel embodiment drawn to "a multiplicity of foreign DNA I molecules" should be limited to producing multiple copies of the same antibody heavy or light chain, but not both. See McKnight Declaration ¶¶ 65-78, Botchan Declaration, ¶¶ 48-62, 1st and 2nd Harris 132 Declarations, 5/21/07 response pp.51-55.

Examiner Response:

These arguments were considered but not deemed persuasive.

Initially it is noted that in response to the owner's arguments against the reference(s) individually, one cannot show nonobviousness by attacking reference(s) individually where the rejections are based on combinations of references. In this regard the rejection combines the *Axel* teaching of co-expressing separate proteins in a single eukaryotic host in the context of producing an antibody, with the Cabilly 1 patent teaching in combination with the secondary references, especially those suggesting single host eukaryotic co-expression of light and heavy chains.

It is also noted that the selection of an antibody as one or more (multiplicity) of the foreign protein(s) encoded by DNA I is a patented embodiment (see *Axel* patent claims 7, 23, 29, 37, 60 etc.).

The *Axel* patent claims are presumed valid under 35 U.S.C. § 282 unless invalidated by "clear and convincing" evidence and additionally references are presumed to be operable and enabled. See MPEP § 2121 at 2100-64 to 2100-67. Further, the threshold for enabling a prior art reference is lower than the threshold for enabling a patent claim under 35 USC 112, first paragraph. See *Rasmusson v. Smithkline Beecham Corp.* 75 USPQ2d 1297 (Fed. Cir. 2005); and *Impax Labs., Inc. v. Aventis Pharmaceuticals, Inc.*, No. 05-1313 (Fed. Cir. Nov. 20, 2006) concurring with the *Rasmusson* holding.

Initially, it is admitted by the patent owner that the *Axel* reference method already teaches co-expression of two different proteins encoded by foreign DNA I and foreign DNA II in a single eukaryotic host cell.

However, the patent owner argues, that to the extent that the *Axel* claims recite antibody, the claimed antibody should be interpreted to mean antibody chain (heavy or light) and not the entire protein.

The patent owner's interpretation of the meaning of the term "antibody" is contrary to the plain meaning of this term and additionally fails to consider the *Axel* reference teaching taken as a whole to one of ordinary skill in the art. The *Axel* patent clearly possesses the concept of co-transforming a single eukaryotic or mammalian host cell to express functional proteins.

Axel's invention as described and claimed is as follows:

> The present invention relates to processes for inserting DNA into eucaryotic cells, particularly DNA which includes a gene or genes coding for desired proteinaceous materials for which no selective criteria exist. The insertion of such DNA molecules is accomplished by cotransforming eucaryotic cells with such DNA together with a second DNA which corresponds to a gene coding for a selectable marker. The invention further relates to processes for inserting into eucaryotic cells a multiplicity of DNA molecules including genes coding for desired proteinaceous materials by cotransformation with the desired genes and with amplifiable genes for a dominant selectable marker in the presence of successively higher amounts of an inhibitor. Alternatively, the insertion of multiple copies of desired genes is accomplished by transformation using DNA molecules formed by ligating a DNA molecule including the desired gene to a DNA molecule which includes an amplifiable gene coding for a dominant selectable phenotype such as a gene associated with resistance to a drug in the presence of successively higher amounts of an agent such as a drug against which the gene confers resistance so that only those eucaryotic cells into which multiple copies of the amplifiable gene have been inserted survive (emphasis provided). See *Axel* Abstract, emphasis provided.

Additionally, the Following *Axel* Definitions Are Pertinent:

1. "*Cotransformation* means the process for carrying out transformations of a recipient cell **with more than one different gene**". Axel '216 patent col. 4, lines 23-25 (with emphasis). Cotransfromation is synonomous with coexpression.
2. "*Proteinaceous* material means any **biopolymer** formed from amino acids". Axel '216 patent col. 4, lines 28-30, with emphasis
3. "*Interferon* protein means the proteinaceous part of the glycoprotein interferon, that is, the **portion remaining after removal of the sugar portion**." Axel '216 patent col. 4, lines 47-52, with emphasis.

Accordingly, the above *Axel* Abstract and definitions suggest co-transforming more than one desired gene for making proteinaceous materials which include multimeric proteins, such as interferon. The *Axel* disclosure further supports this interpretation.

As described by *Axel*, the use of eukaryotic host cells for protein expression overcomes prokaryotic host cell expression obstacles including the presence of bacterial toxins and the prokaryotic host cell inability to effect post-translation

modifications including *covalent modifications* and additionally glycosylation. See *Axel* col. 2,lines 42-66 for insulin covalent modification; and col. 3, lines 1-20 for interferon covalent modification and glycosylation.

Particularly, the *Axel* method extends the prior art ability to express foreign selectable phenotypes in eukaryotic mammalian cells (citing *Wigler, M., et al.*, Cell 11: 223-232 (1977); *Axel* col. 2, lines 16-19) to cotransformation with the addition of a foreign DNA which "... can be expressed by the cotransformants **to generate functional proteins.**" (*Axel* col. 2, lines 19-32, with emphasis). Preferred proteinaceous materials include multimeric proteins particularly "... interferon protein, antibodies, insulin, and the like" (Axel col. 2, lines 34-36) in which the Axel method is advantageously employed:

> The present invention provides major advances over bacterial systems for future use in the commercial preparation of proteinaceous materials particlarly proteins of eucaryotic origin such as *interferon protein, antibodies, insulin*, and the like. Such advantages include the ability to use unaltered genes coding for precursors for such proteinaceous materials. After cellular synthesis, the precursor can be further processed **or converted within the eucaryotic cell to produce the desired molecules of biological significance** (col. 2, lines 39-41: with emphasis).

From the above description, it is clear that *Axel's* claims directed to the coexpression in a single eukaryotic host of proteinaceous materials, which include an antibody (as well as insulin and interferon), is referring to the plain meaning of the term "antibody" as representing a "functional" antigen-binding immunoglobulin molecule containing at least the variable portions of the heavy and light chain.

Further, the *Axel* reference suggests expressing two immunoglobulin chains in a single eukaryotic host cell, since *Axel* discloses and claims encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains. The *Axel* reference clearly encompasses one or more genes which encode one or more proteins: e.g. "... DNA which includes a gene or genes coding for desired proteinaceous materials ..." (Abstract lines 1-4, with emphasis). Accordingly, *Axel's* patented multiplicity of foreign

proteins encompasses the expression of the same (antibody light or heavy chain) or different proteins (antibody light and heavy chains) resulting in a functional antibody.

7. In rebutting the Rice and Baltimore article teaching, the Patent Owner notes difficulties regarding lymphocyte antibody production as of early April 1983 including:

a. the uncertainty of the lymphocyte antibody producing mechanism and the ability to control expression of light chain in B lymphocyte cell lines; and
b. the genetic engineering of a relatively small number of recombinantly produced multimeric proteins such as an immunoglobulin tetramer
that would preclude the extension of "individual chain expression procedure" to co-expression of light and heavy chains with "any degree of confidence".Botchan Dec ¶72.

See Oct. 30 '06 response pp. 32-35; 2nd Dr. Harris Declaration (¶¶ 8-28); 2nd Dr. Rice Declaration (¶¶ 8-16).

Examiner Response:

These arguments and declaration evidence are not persuasive.

Regarding item a. above, knowledge of mechanism (e.g., the factors that regulate immunoglobulin expression), is not always complete, or even known prior to practicing a claimed invention. Additionally, with respect to uncertain variables including uncharacterized control elements or possible influence by continued heavy chain expression discussed in the Rice and Baltimore article, it is noted that scientific experimentation always involves unknown parameter(s).

With regard to item b. above, it is noted that it was already known in the art that heavy and light chains of native antibodies are expressed in a single B cell. Additionally, it was well within the skill of the art to obtain appropriate coding sequences for both antibody chains and transform a competent eukaryotic host cell. Accordingly, the *Rice and Baltimore* teaching of successfully cloning a light chain into a heavy chain producing B lymphocyte that secretes assembled antibody would provide ample motivation to clone both light and heavy chains into an analogous competent eukaryotic host cell with a reasonable expectation of success.

Additionally, the patent owner's analysis of the state of the prior art as of April 1983 regarding genetic engineering in the context of expressing proteins, including

immunoglobulins is incomplete. For example, the *Cabilly 1* patent disclosure describes the "state of the prior art"" as follows:

> Recombinant DNA technology has reached sufficient sophistication that it includes a repertoire of techniques for cloning and expression of gene sequences. Various DNA sequences can be recombined with some facility, creating new DNA entities capable of producing heterologous protein product in transformed microbes and cell cultures. The general means and methods for the *in vitro* ligation of various blunt ended or "sticky" ended fragments of DNA, for producing expression vectors, and for transforming organisms are now in hand. ... In practice the use of recombinant DNA technology can express entirely heterologous polypeptides-so called direct expression-or alternatively may express a heterologous polypeptide fused to a portion of the amino acid sequence of a homologous polypeptide. .... The art of maintaining cell or tissue cultures as well as microbial systems for studying genetics and cell physiology is well established. Means and methods are available for maintaining permanent cell lines, prepared by successive serial transfers from isolated cells. For use in research, such cell lines are maintained on a solid support in liquid medium, or by growth in suspension containing support nutriments. Scale-up for large preparations seems to pose only mechanical problems. See Cabilly 1 patent '567, col. 4, lines 8-54.

Further, as admitted in the patent owner submitted "Declaration of Dr. Richard Axel" provided in the related 08/422,187 [1] patent application in response to an enablement rejection, the Cabilly 1 patent specification examples drawn to procaryotic *E. coli* host cell expression of individual immunoglobulin chains was asserted to be applicable to a variety of other host cell types including eukaryotic host cells e.g. yeast, VERO, HeLa, Chinese Hamster Ovary or CHO, W138, BHK, COS-7 and MDCK.

Thus, the tools available to one of ordinary skill in the art include the above background teaching in addition to prior art reference teachings directed to recombinant expression and/or recovery of one or more heterologous proteins (including immunoglobulins and Fv or Fab fragments) in prokaryotic and eukaryotic hosts.

8. Regarding the Rice and Baltimore PNAS article, Dr. Rice in his 1st and 2nd declarations state that the article's purpose was to gain a better understanding of mechanisms by which differentiated B cells regulate immunoglobulin expression. The

[1] The 08/422,187 application is a continuation of 07/205,419 application which is the instant patent undergoing reexamination.

article does not explain how one might produce exogenous heavy and light chain in the 81A-2 strain which already endogenously produced heavy chain since the article fails to clearly demonstrate that tetrameric antibody assembly resulted in a functional antibody. See 10/30/06 Owner response pp.51-53; 2nd Dr. Rice Declaration Rice ¶¶ 46-58, 64; May 21, 2007 response pages 41-43; Owner 5/21/07 response pp. 40-43.

Examiner Response:

This argument is not persuasive.

Initially, it is noted that the arguments are not commensurate to the instant Cabilly patent claims that are not specifically limited to the feature upon which the patent owner relies e.g., properly assembled "functional" antibody. The term "immunoglobulin" in the instant methods, as discussed in the above claim interpretation section, represents a generic term that encompasses both specific (i.e. antibodies) and non-specific immunoglobulin proteins e.g. produced at low levels by lymph or myelomas. See Cabilly 2 patent col. 1, lines 23-43.

In any event, the *Rice and Baltimore* reference clearly teaches eukaryotic host cell expression and secretion of assembled IgG2b tetrameric antibody, even though both chains possess different antigen specificity.

Thus, in light of the *Rice and Baltimore* teaching, it would be reasonable for one of ordinary skill in the art to expect that expressing a light and heavy chain of the same antigen specificity in a competent host would result in the assembly of a functional antibody. See *Declaration of David Baltimore* submitted by the 3rd party with the 2nd Request for Reexamination.

9. The Examiner improperly relied upon a 3rd Party Opinion Declaration of Dr. David Baltimore in this Ex Parte *Reexamination since the reexamination statute limits the determination of a Substantial New Question of Patentability (SNQ) to "patents and printed publications" citing In re Lonardo.*

Examiner Response:

This argument is not persuasive.

"[A]ffidavits or declarations (or other written evidence) which explain the contents or pertinent dates of prior art patents or printed publications in more detail may be

considered in reexamination ... " See MPEP 2258 (I)(E): "Affidavits or Declarations or Other Written Evidence"

Additionally, it is proper to submit affidavits under 37 CFR 1.132 or cite references to show what one skilled in the art knew at the time of filing the application. A declaration or affidavit is, itself, evidence that must be considered. The weight to give a declaration or affidavit will depend upon the amount of factual evidence the declaration or affidavit contains. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); MPEP 2164.05 and MPEP 2124.

The above-recited rejection is proper as it relies solely on patents and printed publications and not Dr. Baltimore's Declaration. The evidentiary use of Dr. Baltimore's declaration is proper since it is being offered only to explain the interpretation of the contents of a prior art printed publication e.g. the teaching as a whole of the Dr. Rice and Dr. Baltimore 1982 PNAS article to one of ordinary skill in the art.

10. *Dr. Baltimore's opinion regarding obtaining a functional antibody is not credible since he is not representative of one of ordinary skill in the art since he is "extraordinary" (Nobel Laureate) and thus has a "unique perspective"; and his opinion is merely conclusory. Additionally, the article's "individual chain expression procedure" would not be deemed extrapolatable to coexpression of both chains resulting in secretion of assembled function antibody since:*

a. "work done in hybridomas and other stable lymphocyte cell lines ... would have led a molecular biologist to conclude that how and when heavy and light chain genes were expressed in the cell would affect the assembly of an immunoglobulin tetramer ...". Bothchan Declaration ¶ 71(references cited therein including Kohler, PNAS USA 77(4): 2197-2199 (1980)); and
b. "Dr. Baltimore's statement also seems inconsistent with the skepticism reflected in papers by other scientists ... reporting findings that suggested that not only was the way immunoglobulin genes were expressed important to the ability of the B-cell to produce properly formed antibodies, it was even important to the viability of the B-cell. For example, Dr. Kohler had reported in 1980 that ... excess heavy chain production could be toxic to the cell, and others reported that many hybridomas spontaneously lose the ability to secrete immunoglobulins or stop expression of one or the two immunoglobulin chains." McKnight Declaration ¶ 90 (citing Kohler, PNAS USA 77(4): 2197-2199 (1980) and Coffino et al. PNAS USA 68: 219-23 (1971)).
See e.g., 3rd Party submitted Dr. Baltimore Declaration; 10/30/06 Owner response pp.51-53; 2nd Dr. Rice Declaration Rice ¶¶ 46-58, 64; 5/21/07 response pp. 41-43.

Examiner Response:

These arguments are not persuasive for the following reasons.

Regarding, Dr. Baltimore's ability to qualify as "one of ordinary skill in the art", It is admitted that "one of ordinary skill in the art" as of early April 1983 is at least "a Ph.D. in molecular biology or a related field, and about two years of post-doctoral experience in a lab working with recombinant DNA." See 2nd Dr. Rice Declaration ¶ 8.

Accordingly, both Dr. Rice and Dr. Baltimore clearly qualify as "one of ordinary skill in the art" and both are authors of the 1982 PNAS article and thus share the same "unique perspective" regarding the subject matter presented thereto. Accordingly, comparable weight is being afforded their respective opinions.

With respect to the weight to be afforded Dr. Baltimore's 132 Declaration in light of the evidence of record the following is noted:

Dr. Baltimore in his declaration states the following:

2. I am one of the authors of Rice et al. Proc Natl Acad Sci, Volume 79, Pages 7862-65 (December 1982)

3. We performed the experiments reported in Rice et al. because of our primary interest in expression of the gene encoding the immunoglobulin chain.

4 In passing, and as part of such experiments, we also determined and reported that the exogenous immunoglobulin light chain expressed in mammalian cells assembled with an endogenous heavy immunoglobulin chain expressed in such cells to produce an intact immunoglobulin protein.

5. We did not perform further experiments to demonstrate that two exogenous chains of a known antibody or one exogenous and one endogenous chain of a known antibody, if produced in the same mammalian cell, would assemble into a functional antibody. However, in light of our demonstration that an introduced light chain gene encoded a protein that would combine with an endogenous heavy chain, without further testing of the idea I and other working in the field would have expected that if two chains were expressed, they would form a functional antibody.

See 90/007859 proceeding dated 12/23/2005 submitted with the request.

Dr. Rice and Dr. Baltimore appear to be in agreement that the studies in the PNAS article provide a demonstration that a functional kappa (light chain) gene can be introduced into a lymphoid cell line in which it is continuously expressed (Dr. Rice Declaration ¶ 55; and Abstract of article).

However Dr. Rice, as well as Dr Botchan and Dr. McKnight, disagree with the following Dr. Baltimore statement:

> ... in light of our demonstration that an introduced light chain gene encoded a protein that would combine with an endogenous heavy chain, without further testing of the idea I and others working in the field would have expected that if two chains were expressed, they would form a functional antibody". See Dr. Baltimore declaration at ¶ 5.

The submitted articles relied upon in the declarations of Dr. Rice, Dr. Botchan and Dr. McKnight for the premise that "individual chain expression procedure" would not be deemed to one of ordinary skill in the art as of early 1983 to be extrapolatable to coexpression of both chains to achieve secreted, assembled functional antibody is not persuasive.

Regarding the *Kohler* article toxicity problem resulting from B-lymphocyte excess heavy chain expression the following is noted. Initially, B-lymphocytes normally produce functional antibody and normally (as dictated by natural selection) excess light chain and not excess heavy chain is produced. See *Kohler* at page 2197, left column. Accordingly, lethality occurring from excess heavy chain expression is not the norm but the exception. In this respect, there is no prior art evidence of record that co-transformation in lymphocytes or other eukaryotic host cells would have been expected to result in the exceptional over-production of heavy chain and lymphocyte toxicity.

The *Coffino* article is similarly non-convincing. Coffino measured the rate of somatic mutation in immunoglobulin production by mouse myeloma cells and found that occasionally (<15% of colonies) mutation variants resulted in the loss of the ability to produce both H and L chains. See Coffino Abstract; page 222 "Discussion". Again, successful lymphocyte immunoglobulin H and L expression and secretion of functional antibody is the norm, while mutation is the exception. In this regard, there is no prior art evidence of record that co-transformation in lymphocytes or other eukaryotic host cells would have been expected to result in increased incidence of mutation.

Similarly, the other articles referenced in Dr. Botchan's declaration at ¶ 71 fail to

provide definitive evidence that precludes a reasonable expectation of extrapolating the *Rice and Baltimore* article's teaching of lymphocyte secretion of assembled antibody to co-expression of a compatible eukaryotic host.

Additionally, it is again noted that in response to the owner's arguments against the reference(s) individually, one cannot show nonobviousness by attacking reference(s) individually where the rejections are based on combinations of references.

In this regard, the *Ochi* reference by using a different eukaryotic host cell, *restored antibody function* by cloning a light immunoglobulin chain into a cell line endogenously producing heavy immunoglobulin chain of the same specificity. Additionally, *Axel* further teaches eukaryotic co-expression resulting in functional proteins, including antibodies.

Thus, in view of the totality of the evidence, including the *Rice and Baltimore* article, and the prior art of record, Dr. Baltimore' opinion regarding the reasonable expectation of successfully expressing light and heavy antibody chains in a single eukaryotic host cell is credible.

11. Ochi is at best cumulative to the Rice and Baltimore 1982 PNAS paper since it uses a cell line that was already producing an endogenous light chain protein. Even though the Ochi experimental protocol was more certain (than the PNAS lymphocyte line) since their host cell retained the ability to endogenously produce heavy and light chain, Ochi nevertheless achieved "abnormal levels of expression". The Oi report of "varying levels of expression" in their hybridoma cell lines casts doubt on the ability to successful express antibody heavy and light chains. Functional assembly of an immunoglobulin tetramer in lymphocytes is questioned in view of the lack of information regarding the control of light chain expression levels in lymphocytes. See 10/30/06 owner response pp. 38-41; 2nd Harris Declaration ¶¶ 79-86; 2nd Rice Declaration ¶¶ 21-26; Botchan Declaration ¶¶ 95-106.

Examiner Response:

These arguments are not persuasive.

Regarding variability in gene expression, as discussed in *Ochi* between transformed and wild type B-cells, it is noted that scientific experimentation always involve unknown parameter(s).

Ochi is not cumulative to the *Rice and Baltimore* article teaching, since as admitted by the patent owner, *Ochi* confirmed that transforming a mammalian host expressing heavy chain with a light chain having the same antigen specificity (specific for TNP) results in the successful assembly of a *functionally* secreted antibody (specific for TNP).

Similarly, *Oi* successfully transformed a hybridoma producing heavy chain with a light chain to produce a secreted assembled *intact* antibody.

Accordingly, the *Ochi* and/or *Oi* references provide additional motivation to co-transform a single mammalian cell with appropriate light and heavy antibody chains with a reasonable expectation of producing secreted, assembled and functional antibody.

This result is consistent with the *Axel* teaching (eukaryote host) and the *Moore* teaching (prokaryote and yeast hosts) that assembly of recombinantly produced light and heavy chains of the same specificity produce functional antibody or antibody fragments (Fab or Fv).

12. Kaplan fails to suggest production of multiple immunoglobulin chains in one transformed host cell. The suggestion regarding construction of recombinant DNA molecules containing either an antibody heavy chain or an antibody light chain gene, expressing these genes in separate cells, and assembling the light and heavy chain proteins is not supported by experimental results, examples or specific guidance regarding these methods of producing a heavy or light immunoglobulin chain polypeptide. See 10/30/06 Owner response pp 53-54; Harris Second Declaration, ¶ 69; Botchan Declaration ¶¶ 73-77; McKnight Declaration ¶¶ 92-96.

Examiner Response:

This argument is not persuasive.

The above rejection is relying on the combined teaching of multiple references with the *Kaplan* reference teaching. Accordingly, the failure of the *Kaplan* reference to teach single host cell antibody expression using its recombinantly produced heavy and light chains is not persuasive.

As discussed in the above rejection, *Kaplan* teaches that human hybridomas can serve as a useful source of mRNA encoding the antibody heavy and light chains to specific antigens. By using known molecular biology techniques, the mRNA's can be

used for the generation of genes which, when inserted into the appropriate vector, can serve as a coding source for the production of proteins (see p.3, lines 4-9). Further, *Kaplan* teaches that a variety of host cells (bacteria and yeast) and plasmids (particularly pBR322) may be used to recombinantly express heavy and light chains (see p.10, lines 1-33).

Accordingly, although *Kaplan* fails to exemplify the recombinant making of antibodies, *Kaplan* nevertheless provides a road map to one of ordinary skill in the art as to how to do so. Thus, *Kaplan* is not limited to dependent claims drawn to the use of hybridomas, plasmids or host cells (as implied by the patent owner), but is additionally relevant to enable co-expressing light and heavy chains in a competent host cell (prokaryotic, eukaryotic or otherwise) to obtain an assembled functional antibody.

13. Dallas is limited to teaching the expression of "simple" bacterial genes in bacterial host cells (E.Coli) which differs from the expression of eukaryotic genes in bacterial cells. Eukaryotic immunoglobulin genes are more complex than bacterial genes which lack introns and bacterial gene control elements and translational control elements were far better characterized and understood in early 1983 relative to eukaryotic systems. Additionally, the proteins produced by Dallas are "small simple polypeptides" that are apparently not secreted by or recovered from the host cells. See 10/30/06 response pp.54-56; 1st Dr. Rice declaration ¶ 42; 5/21/07 response pp.48-49; Dr. Botchan declaration ¶¶ 78-83; Dr. McKnight Declaration ¶¶ 97-102.

Examiner Response:

This argument is not persuasive.

Initially, the owner concedes the relevancy of the *Dallas* references teaching toward prokaryotic expression within the instant claim scope.

However, regarding both prokaryotic and eukaryotic expression, the owner fails to appreciate the significance of the *Dallas* reference teaching when combined with the teachings of the other prior art references of record.

As pointed out in the above rejection, *Dallas* teaches that two different proteins (in addition to a selectable marker) can be expressed in a single host cell and such expression may be accomplished by the use of two vectors, each containing DNA

encoding one of the proteins, or by use of a single vector that contains DNA encoding each of the proteins.

Accordingly, the *Dallas* reference is relevant toward modifying the *Cabilly 1* and other prior art methods, including *Moore*, to co-express (using one or two vectors) a light and heavy antibody chain in a competent prokaryotic or eukaryotic host cell.

Additionally, *Dallas* supports the *Axel* reference teaching of eucaryotic expression of both light and heavy antibody chains along with the reporter gene for producing an antibody. In this regard *Axel* specifically provides motivation to utilize eukaryotic hosts, in preference to prokaryotic hosts (as in *Dallas*), for expressing two or more exogenous proteins.

14. Regarding Axel, Rice, Kaplan or Dallas , it is "striking" that none of these references expressly teach producing immunoglobulin molecules or functional fragment by independently expressing, in a single host cell, DNA sequences encoding both light and heavy immunoglobulin chains". See Oct. 30, 2006 response p.39; 2nd Dr. Harris and 2nd Dr. Rice Declarations.

Examiner Response:

This argument is not persuasive since anticipation by the *Axel, Rice, Kaplan or Dallas* references is not at issue.

15. Deacon (1976) ('82 Valle cumulative) and Valle (1981), employ an "experimental model system" (the Xenopus oocyte cell) which is an undifferentiated frog egg cell which upon fertilization differentiates into all the different types of cells. The Xenopus oocytes which employ messenger RNA (mRNA) are not representative of the instantly claimed "host cells" in light of their special capacity to translate mRNA relative to differentiated cells utilizing a vector. Thus, one skilled in the art would not consider frog cells, "host cells" within the meaning of the instant claims. See 10/30/06 Owner response pp. 38-62; 5/21/07 response pp. 65-72; Colman Dec.; 2nd Harris Dec. ¶¶ 87-97; Botchan Dec. ¶¶ 84-94; McKnight Dec. ¶¶ 103-105 and 109-113.

Examiner Response:

These arguments are not persuasive.

As described in the rejection, *Deacon (1976)* teaches injecting mRNA encoding heavy and light immunoglobulins (to hemocyanin or ferritin antigen) into eukaryotic

Xenopus (frog) oocytes for successful translating and secreting of assembled functional antibody.

The *1981 and 1982 Valle* references confirm the *Deacon* teaching by microinjecting mRNA encoding light (kappa) and heavy (gamma 1) immunoglobulin chains into *Xenopus* oocytes to produce secreted assembled functional tetrameric mouse antibody.

As defined in the Cabilly 2 patent (col. 8, lines 26-28), "Host cells," include prokaryotic or eukaryotic cells, such as eukaryotic microbes, and cells derived from multicellular organisms, such as mammalian cells. See '567 patent, col. 8, line 46 to col. 10, 1ines 13-30, 57. Accordingly, frog (as amphibians, vertebrates) eggs are within the scope of the term "host cells".

To the extent that the owner argues that that the *Deacon* and *Valle* references fail to teach transforming a *Xenopus* host with DNA, e.g. by using a vector(s), to obtain a transformed host cell, the Examiner acknowledges this deficiency that prevents the *Deacon* and *Valle* references from being anticipatory.

As pointed out in the rejection, the teachings of the *Deacon (1976), Valle (1981)* and/or *Valle (1982)* references do not depend upon the genetic material used, since once expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression.

Recombinant production of an exogenous protein necessarily involves transcription of the exogenous DNA to produce exogenous mRNA. The exogenous mRNA is then translated into exogenous protein. See *1982 Valle* Abstract.
In this respect, frog eggs and oocytes were recognized models for determination and measurement of m-RNA protein translation. See e.g.*Gurdon et al.*, Nature 233, (9/71) pages 177-182. Additionally, it was experimentally established that oocytes can transcribe injected DNA into m-RNA and achieve functional protein expression. *Gurdon and Melton*, Ann. Rev. Genet. 13:189-218 at 197-198 (1981).

Accordingly, in the context of obviousness, the *Deacon (1976)* and *Valle* (1982) references suggest that modifying the genetic material (from mRNA to DNA) encoding antibody heavy and light chains for transforming a competent eukaryotic host would

reasonably be expected to achieve expression (transcription and translation) and assembly of functional immunoglobulin. Based on such teachings, it would have been obvious to one of ordinary skill in the art to perform the *Cabilly1* patented method in a single host cell to produce an immunoglobulin.

In this regard, the patent owner has failed to prove that successful transformation using an undifferentiated eucaryotic host cell (xenopus oocyte) would not be reasonably expected to work in a differentiated eukaryotic cell in an analogous manner.

Moreover, it is noted that the patent owner's past action during an opposition proceeding in Europe provides evidence that undermines the owner's present argument.

In Europe, one of the owners of Cabilly 2 (Genentech, Inc.) opposed a European patent granted to Celltech Limited (the "Boss Patent") that contained the following claim:

> A process for producing a heterologous Ig molecule or an immunologically functional Ig fragment in a single host cell, which comprises transforming the host cell with separate DNA sequences respectively encoding polypeptide chains comprising at least the variable domains of the Ig heavy and light chains and expressing each of said polypeptide chains separately in said transformed single host cell. [See Appendix C, p. 1, A.1.1 provided by the 3rd party requester in the 90/007,859 proceeding]

The challenged Boss patent claim is essentially identical to claim 1 of the instant invention and in the opposition, Genentech asserted that the Boss claims were not patentable (lacked novelty or inventive step) over the *1982 Valle* reference teaching. In particular, Genentech stated:

> 2.3 Accordingly, Document 2 (Valle) clearly teaches the production of an immunologically functional heterologous immunoglobulin molecule in eukaryotic cell transfected by separate DNA molecules encoding its heavy and light chains, respectively. In view of the broad implications evidenced by the Abstract, the fact that the actual experiment was performed with microinjected mRNAs is not relevant. In any event, because the messenger RNA carries the information from DNA to the ribosomal sites of protein synthesis, it is functionally equivalent to DNA.

Accordingly, the patent owner's use of the *Valle (1982)* reference teaching in the opposition against claim(s) analogous to those of the instant patent would constitute an evidentiary admission that immunoglobulin expression in an undifferentiated eucaryotic host cell (i.e. *xenopus oocyte*) would be correlative to host cell immunoglobulin expression within the scope of the instantly claimed invention.

16. The Genentech attorney statement in the EPO Opposition of the Boss patent proceeding submitted by the 3rd Party in the instant request is outside the scope of this reexamination since "{A] third party ... may not submit admissions of the patent owner outside the record" citing MPEP 2258(I)(F). Additionally the Examiner improperly viewed the owner attributed statements regarding the 1982 Valle reference as an owner admission since it is "not an admission as to a fact, but mere attorney argument" which was factually incorrect as explained by the newly submitted Dr. McKnight Declaration:

> The statement cited by the Office is plainly not a factually correct statement. For example, as Dr. McKnight explains, the statement in the pleading that Valle "clearly teaches the production of an immunologically functional heterologous immunoglobulin molecule in eukaryotic cell transfected with separate DNA molecules encoding its heavy and light chains respectively" is factually incorrect. McKnight Declaration, ¶ 107. As he points out, Valle 1981 (and Valle 1982.) did not use DNA in their experiments, but mRNA. He also explains that the hypothesis that mRNA is "functionally equivalent" is factually incorrect, as a scientific matter, given that mRNA has the function of facilitating translation of genetic information into polypeptide sequences, while DNA has the function of storing genetic information for passage to progeny of the cell.

McKnight Declaration, ¶¶ 107-108; 5/21/07 response pp. 72-73; MPEP 2258(I)(F).

Examiner Response:

Initially it is noted that the use of patent owner admissions, from whatever source, for purposes of patentability is proper. In this respect, MPEP 2253 (scope of reexamination) sanctions the examiner's use of owner admissions, including that obtained from the specification *or legal proceedings*, for patentability purposes, especially factors concerning the obviousness inquiry. See 37 CFR 1.104 (c) (3). To ignore an admission by the patent owner and not use the admission as part of the prior art in conjunction with patents and printed publications in reexamination would make it impossible for the examiner to properly determine the scope and content of the prior art. See *Ex parte Seiko Koko Kabushiki Kaisha*, 225 USPQ 1260 (Bd. Pat. App. & Inter.

1984); *Ex parte Kimbell*, 226 USPQ 688 (Bd. Pat. App. & Inter. 1985); and in *Ex parte McGaughey*, 6 USPQ2d 1334 (Bd. Pat. App. & Inter. 1988); *In re Nomiya*, 509 F.2d 566, 184 USPQ 607 (CCPA 1975); MPEP 2253 (emphasis provided).

In the present instance, as part of the request for reexamination, the 3rd party requester submitted the Genentech attorney statement in the EPO Opposition of the Boss patent proceeding as being relevant to a substantial new question of patentability (SNQ) relating to the teachings of the Deacon (1976) and Valle (1981 and 1982) prior art references.

MPEP 2258 (I)(F) **Section 1** addressing "Initial Reexamination Determination and Order", specifically permits 3rd party submission of patent owner admission(s) of record in the file *or in a court record* in association with prior art reference(s) for establishing a substantial new question of patentability:

> "The consideration under 35 U.S. C. 303 of a request for reexamination is limited to prior art patents and printed publications ... [t]hus an admission, *per se*, may not be the basis for establishing a substantial new question of patentability. However, an admission by the patent owner of record in the file **or in a court record** may be utilized in combination with a patent or printed publication" (emphasis provided).

The patent owner's quotation to MPEP 2258(I)(F) is taken from Section 2 which is referring to 3rd party submissions presented after the Reexamination has already been ordered which is outside the scope of an *ex parte* proceeding.

Accordingly, consideration of the Genentech attorney statement in the EPO Opposition of the Boss patent proceeding in the instant reexamination proceeding is proper for purposes of an owner admission and in order to properly determine the scope and content of the prior art.

Regarding, the accuracy of the Genentech's attorney statement it is noted that "[w]hile the scope and content of the admission may sometimes have to be determined, this can be done from the record and from the paper file in the same manner as with patents and printed publications". See MPEP 2253.

As described above, in opposition to the Boss claim, Genentech stated:

> 2.3 Accordingly, Document 2 (Valle) clearly teaches the production of an immunologically functional heterologous immunoglobulin molecule in eukaryotic cell transfected by separate DNA molecules encoding its heavy and light chains, respectively. In view of the broad implications evidenced by the Abstract, the fact that the actual experiment was performed with microinjected mRNAs is not relevant. In any event, because the messenger RNA carries the information from DNA to the ribosomal sites of protein synthesis, it is functionally equivalent to DNA.

Regarding the initial part of this statement, Dr. McKnight correctly recognized *an obvious error* presented in **bold** as indicated below:

> "Accordingly, Document 2 (Valle) clearly teaches the production of an immunologically functional heterologous immunoglobulin molecule in eukaryotic cell **transfected by separate DNA molecules** encoding its heavy and light chains, respectively.

The error's obviousness is readily apparent in view of the remaining statement that correctly refers to the use of "microinjected mRNA" and not "separate DNA molecules".

Dr. McKnight's statement regarding the difference between mRNA and DNA function e.g., mRNA carries the DNA information to the ribosome, is indeed true.

However, the "functional equivalency" aspect of the above owner admission is directed toward the "reasonable expectation of success" prong of the obviousness inquiry as it relates to the analogous use of DNA (instead of mRNA) for expressing immunoglobulins in competent eukaryotic hosts. In this respect, the crux of the above admission is that one of ordinary skill in the art, substituting DNA, for *Valle's* mRNA, for transforming competent eukaryotic hosts would reasonably expect successful secretion and reconstitution of an antibody as realized in the *Valle* reference model system.

17. Kaplan, Builder and Accola references are not directed to transforming or refolding of immunoglobulin heavy and light chains. See 10/30/06 owner response pp. 67-69.

Examiner Response:

In response to the owner's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The obviousness double patenting rejection addresses the application of these references to the instant claim limitations e.g. claims 10, 14, 22 and 27-32.

18. Regarding dependent claim 12, the Cabilly 1 patent teaches making chimeric antibody light and heavy chains with different sources of variable and constant chains and no prior art reference renders obvious the use of same source constant and variable chains. See Oct. 30 '06 response at pages 68-69.

Examiner Response:

This argument is not persuasive because the obviousness double patenting rejection provides a rationale for the obviousness of claim 12 combining the *Cabilly 1* patent claims with the secondary prior art references, e.g. *Kaplan and Rice,* which illustrate the use of "same source constant and variable chains".

Relevant Document(s) Not Relied Upon For A Rejection:

1. *Harvard Journal of Law & Technology* 17(2) (Spring 2004), pp. 583-618:

The Harvard article describes the extensive licensing of the *Axel* patent to over 30 companies (including Genentech) who were recombinantly producing 29 protein drugs (23 proteins of which were specifically claimed by *Axel* including antibodies). This document thus provides evidence that one of ordinary skill in the art interpreted the *Axel patent* claims as being directed to functional proteins, including antibodies. See, enclosed, *Harvard Journal of Law & Technology* 17(2) (Spring 2004), pp. 583-618; at pp. 583-590 (background of Axel patent); pp. 591-593 and Appendix A for licensing.

Conclusion

Claims 1-36 of U.S. Pat. No. 6,331,415 are rejected.

All claims are drawn to the same invention claimed in the proceeding prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the proceeding prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued reexamination and the submission under 37 CFR 1.114. See MPEP § 706.07(b).

A shortened statutory period for response to this action is set to expire two months from the mailing date of this action. Extensions of time under 37 CFR 1.136(a) do not apply in reexamination proceedings. Extensions of time in reexamination proceedings are provided for in 37 CFR 1.550(c). A request for extension of time must be filed on or before the day on which a response to this action is due, and it must be accompanied by the petition fee set forth in 37 CFR 1.17(g). The mere filing of a request will not effect any extension of time. An extension of time will be granted only for sufficient cause, and for a reasonable time specified.

The filing of a timely first response to this final rejection will be construed as including a request to extend the shortened statutory period for an additional month, which will be granted even if previous extensions have been granted. In no event, however, will the statutory period for response expire later than SIX MONTHS from the mailing date of the final action. See MPEP § 2265.

Ongoing Duty To Disclose

The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,331,415 throughout the course of this reexamination proceeding. The third party requester(s) is (are) also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS

Effective May 16, 2007, 37 CFR 1.33(c) has been revised to provide that:

The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

> *Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination*, 72 FR 18892 (April 16, 2007)(Final Rule)

The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.

This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.

In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is strongly encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

Future Correspondences

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah D. Jones can be reached on 571-272-1535.

Direct correspondences relating to this ex parte reexamination proceeding:

By U.S. Postal Service Mail to:

Mail Stop Ex Parte Reexam
ATTN: Central Reexamination Unit
Commissioner for Patents
P. O. Box 1450
Alexandria VA 22313-1450

By FAX to: (571) 273-9900
Central Reexamination Unit

By Hand to: Customer Service Window
Randolph Building, Lobby Level
401 Dulany Street
Alexandria, VA 22314

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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